Continuous Hyperfractionated Accelerated RadioTherapy – Escalated Dose (CHART-ED): A Phase I study

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Abstract

Introduction

Patients who present with locally advanced inoperable non-small cell lung cancer (NSCLC) may be suitable for radical radiotherapy. A randomised trial of 563 patients compared CHART and conventional radical radiotherapy (60Gy/30f) given over 6 weeks and suggested that CHART resulted in a 9% improvement in 2-year survival[1]. RT dose escalation for both conventional and CHARTWEL (CHART-WeekEndLess) - fractionation schedules is feasible with modern 3-dimensional CT-based planning techniques and we initiated a phase I CHART dose escalation study in 2009. **Methods**

Patients with WHO performance status 0-2 histologically confirmed, inoperable, stage I-III non-small cell lung cancer were recruited into an open phase I dose escalation trial. Three cohorts of six patients were recruited sequentially. Total dose was escalated from standard CHART radiotherapy of 54 Gy/36f/12 days to 57.6Gy (2 x 1.8 Gy fractions on day 15, Group 1), 61.2Gy (4 x 1.8 Gy fractions on days 15-16, Group 2) and 64.8Gy (6 x 1.8 Gy fractions on days 15-17, Group 3).

Results

Between April 2010 and May 2012, 18 patients were enrolled from 5 UK centres and received escalated dose radiotherapy. 14 were male, 16 squamous cell histology and 12 were stage IIIA or IIIB. The median age was 70 years and baseline characteristics were similar across the three dose cohorts. One patient did not start escalated radiotherapy but all remaining patients completed their planned radiotherapy schedules. Of these 9 patients have died to date with a median survival of 2 years across the three cohorts. Grade 3 or 4 adverse events (fatigue, dysphagia, nausea and anorexia – classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0) were reported in 6 patients but the pre-specified dose limiting toxicities (grade 4 early oesophagitis; grade 3 cardiac, spinal cord and pneumonitis) were not observed.

Conclusions

CHART remains a radiotherapy schedule in routine use across the UK and in this dose escalation study no dose limiting toxicities were observed. We feel the dose of 64.8Gy / 42f / 17 days should be taken forward into further clinical trials. The sample size used in this study was small so we plan a randomised phase II study that includes other radiotherapy schedules to confirm safety and select an accelerated sequential chemo-radiotherapy schedule to take into phase III studies.

Introduction

Lung cancer is the leading cause of cancer mortality worldwide with approximately 38,000 new cases diagnosed annually in the UK alone[2]. Non-Small Cell Lung Cancer (NSCLC) accounts for approximately 80% of all lung cancers. The majority of cases are inoperable at presentation due to medical co-morbidity (stages I, II and III NSCLC), or tumour extent (stages III and IV NSCLC). Although many patients with stage I-III disease can still be treated radically using radiotherapy the 5 year survival from lung cancer in the UK has changed little (from 3% to 8%) over the last 60 years. The poor outcome can be related to both failure to eradicate local disease and the development of distant metastases. Bronchoscopic re-evaluation after radical thoracic RT has demonstrated persistent tumour in 85% of cases[3]. Successful local control has been found to correlate with improved survival[4]. Approaches to achieve better local control include the acceleration of the RT schedule, the addition of radio-sensitizers and dose escalation[4-6].

Concurrent chemo-radiotherapy (CTRT) (chemotherapy and RT given at the same time) is the standard of care in stage III NSCLC[4] with median survival rates of approximately 21 months. However, the majority of patients are not suitable for this treatment based on poor performance status and co-morbidities[7]. The alternative treatment offered to patients who are unsuitable for concurrent CTRT is sequential CTRT (chemotherapy given prior to RT), but local control rates are inferior when compared to concurrent CTRT which is reflected in worse survival rates[4]. Alternative strategies to achieve improved local control by intensifying the local anti-tumour effect are needed.

In the UK the Continuous Hyper-fractionated Accelerated Radiation Therapy (CHART) trial intensified local treatment by accelerating the RT course. The investigators delivered 54Gy using 1.5Gy fractions 3 times per day for 12 consecutive days (including weekends) and demonstrated an overall survival advantage when compared with the standard fractionation regimen in use at that time (60Gy in 30 daily fractions over 6 weeks)[1]. There was a 9% absolute improvement in 2 year survival (29% v 20%; p=0.004) for CHART with no evidence of a difference in acute or long-term toxicity. This result is supported by an individual patient data meta-analysis[6] confirming that CHART and other intensified schedules which accelerate or hyper-fractionate improve overall survival as compared to conventional fractionation, with an absolute benefit of 3% at 5 years. CHART is currently recommended as the standard radical RT schedule for treating NSCLC in the UK[8]. Despite this improvement in overall survival, persistent local disease remains the main cause of death in patients who received CHART.

RT dose escalation for conventional and the accelerated CHARTWEL fractionation schedules was shown to be feasible with 3-dimensional CT-based planning techniques[9-10]. The initial dose escalation studies delivered additional daily fractions of radiotherapy and the recently completed RTOG 0617 [11] study has shown no benefit for dose escalation with a prolonged treatment schedule. This study compared 60 to 74Gy and reported patients in the higher dose arm suffered higher local relapse rates and inferior survival compared to the control arm.

The RTOG study result is refocusing interest on acceleration and hypo-fractionation and techniques that avoid prolongation of the overall treatment time are attractive as they reduce the impact of accelerated tumour clonogen proliferation, which becomes clinically relevant for NSCLC at least 3-4 weeks after initiation of radiotherapy[12]. Studies have shown that dose escalation using 3-D conformal hypo-fractionated radiotherapy is feasible[13,14] and the application of extreme hypo-fractionation associated with stereotactic ablative radiotherapy (SABR) has delivered impressive local control when used for early NSCLC patients[15]. However, when treating central tumours the toxicity rates associated with SABR were excessive[16]. Due to the short overall duration of the standard CHART schedule, it is possible to dose escalate by introducing additional days of treatment and still complete therapy before the period of accelerated tumour repopulation is expected to begin. This study reports dose escalation beyond standard CHART performed in a stepped approach using additional twice daily 1.8Gy fractions.

Methods and materials

Patients and study design

When the study was designed a pragmatic decision was taken not to give the additional radiotherapy fractions outside the standard working hours for the radiotherapy departments. Radiobiological advice guided us to use twice daily 1.8 Gy fractions estimating that the maximum tolerated dose for oesophagus would be around 65 Gy given over 18 days.

Patients had to have histologically or cytologically confirmed stage I-III non-small cell lung cancer, with disease deemed inoperable disease by a Lung Cancer Multi-Disciplinary Team (MDT) with input from Thoracic Surgeon, or operable but the patient refuses surgery. Patients had to be previously untreated with chemotherapy or radiotherapy, have ECOG performance status 0 or 1, a life expectancy of at least 6 months, be free of any malignancy likely to interfere with protocol treatment or comparisons, have adequate respiratory function (i.e. forced expiratory volume in one second (FEV1) or transfer factor (DLCO) of greater than 40% predicted), and be considered suitable for CHART.

Pre-trial entry, patients had an up to date clinical assessment of eligibility, which included PET-CT, pulmonary function tests, ECG, Haematology and biochemistry tests (with a brain scan if required) performed within 42 days of trial registration. Baseline patient characteristics were collected, and then participating centres telephoned the Scottish Clinical Trials Research Unit, who allocated patients to one of the treatment cohorts. Patients attended for CHART radiotherapy planning as soon as possible after registration and on confirmation that the plan would meet the normal tissue dose constraints the patient attended for treatment verification and to consent to enter the trial.

Radiotherapy Treatment Planning

All patients were 3D-conformally planned and treated in the supine position, with arms supported above the head with an external immobilisation device. A single phase technique was used, without elective nodal irradiation. A planning CT scan using continuous 2.5 - 5mm slices was acquired throughout the entire volume of both lungs in the treatment position. Treatment was planned with full information from bronchoscopy, CT-PET and, if performed, mediastinoscopy or thoracotomy and 3D conformal RT planning used inhomogeneity correction. Treatment planning aimed to optimise the dose distribution to allow dose escalation and dose volume histograms (DVH) were constructed for the planning target volume (PTV), oesophagus, heart, whole lung minus gross tumour volume (GTV), and spinal cord.

Gross Tumour Volume (GTV) included the primary tumour mass and involved nodes, defined as nodes with short axis > 10 mm or showing increased uptake on PET-CT. Clinical Target Volume (CTV) is arrived by expansion of GTV by a 5 mm. Planning Tumour Volume (PTV) is arrived by expansion of CTV by a 10 mm margin (15 mm margin in the cranial caudal direction). Dose was calculated using type B algorithms and prescribed to the ICRU reference point. The specified dose constraints were -

CTV	Minimum dose > 95% of prescribed dose
PTV	$V_{(95\% \text{ of prescribed dose})} > 90\%$
Cord	Maximum dose < 44Gy
Whole Lung-GTV	$V_{(20Gy)} < 35\%$
Oesophagus	Maximum dose < 105% of prescribed dose
Heart	$V_{(100\% \text{ of prescribed dose})} < 30\%$ $V_{(50\% \text{ of prescribed dose})} < 50\%$

Simulation and electronic portal images (EPIs) were used to confirm the accuracy of treatment to within 5mm with set-up should be adjusted according to local guidelines when discrepancy was e 5mm.

Radiotherapy Quality Assurance

Radiotherapy Quality Assurance (QA) was a requirement for all participating centres, and was administered by a central QA group. The QA process built on that developed for the INCH[17] and CONVERT[18] trials in collaboration with the NCRI QA group based at Mount Vernon Hospital. Prior to entering patients centres had to complete a questionnaire covering immobilisation and planning imaging, planning parameters, commissioning the treatment planning system, and treatment delivery facilities. Each clinician had to submit a patient plan and accreditation was only granted once the QA group had approved the plan. Subsequently each local radiotherapy team had to complete a delineation exercise and each centre was visited in order to perform dosimetric and portal imaging QA using phantoms.

Statistical analysis

The dose escalation schedule was -

Group 1	57.6Gy in 38 fractions, treating 8 hours apart on day 15 (CHART plus 2 x 1.8 Gy fractions on day 15)
Group 2	61.2Gy in 40 fractions, treating 8 hours apart on days 15-16 (CHART plus 4 x 1.8 Gy fractions on days 15-16)
Group 3	64.8Gy in 42 fractions, treating 8 hours apart on days 15-17 (CHART plus 6 x 1.8 Gy fractions on days 15-17)

Six patients were recruited sequentially into each Group, providing that the following dose limiting toxicity (DLT, classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0) were not met at the previous dose level:

Pneumonitis:	Grade 3 or above:	More than one patient (out of six)
Cardiac Toxicity:	Grade 3 or above:	More than one patient (out of six)
Spinal Cord Toxicity:	Grade 3 or above:	More than one patient (out of six)
Oesophagitis (Early):	Grade 4 or above:	More than one patient (out of six)

The maximum tolerated dose (MTD) was defined as the dose level below which > 1/6 or > 2/12 patients experience a DLT. If these DLT rates are not observed then the top dose will be recommended.

When 6 patients had been recruited into each of the groups, review ensured that the maximum oesophageal dose lay within +/- 5% of the prescribed dose in at least 4 patients before recruitment proceeded to the next dose level. If dose limiting levels of toxicity were reported for one patient, a further 6 patients were recruited at that dose level to expand the group. Recruitment was interrupted following completion of each group, until at least 4 patients had been followed up for 2 months to ensure that any early oesophageal reactions had settled. If one or more patients developed late pulmonary toxicity of Grade 3 or higher then recruitment into the CHART-ED study would end.

Data were analysed on an intention to treat basis regardless of any deviation from the protocol. Survival was measured from the date of first treatment until the date of death from any cause, with surviving patients censored at the date of their last assessment.

Trial Governance

The trial was approved by the Oxford A Medical Research Ethics Council (MREC), and all patients provided written informed consent. The trial was conducted in compliance to the principles outlined in the Medical Research Council Good Clinical Practice (MRC GCP) guidelines and the Data Protection Act (DPA G0027154) and other regulatory requirements.

Results

Nineteen patients were recruited into the study, one received the standard CHART dose and fractionation but did not receive the planned dose escalation on day 15. This patient in cohort three, suffered an exacerbation of COPD as the CHART schedule was being completed. A further patient was recruited to this cohort and all other patients received the planned radiotherapy treatment on schedule. The baseline demographical details are recorded in Table 1, and radiotherapy planning details summarised in table 2.

No patient experienced the pre-specified dose limiting toxicities though 6 patients did report grade 3 – 4 adverse events (fatigue 3, dysphagia 3, anorexia 3 and nausea 1). Figure 1 shows the doses received by the oesophagus and acute oesophagitis was documented in 17 of the patients treated, generally grade I – II but three patients required iv hydration (Grade 3 oesophagitis). Late oesophageal toxicity has been limited to grade I/II in 5 patients. Grade I pulmonary pneumonitis / fibrosis was documented (clinically or radiologically) in 12 patients across the three cohorts and no cardiac or spinal cord toxicity was reported though one cardiac arrest was documented 12 months after completion of radiotherapy.

A tumour response was documented in 11/18patients (61%) across the cohorts (complete response in 5/18 (28%) patients and a further 5 patients had stable disease on post-treatment CT scans. After a median follow up time of 21 months (range 1 – 36) 8 patients had relapsed, 3 with only loco-regional progression.Nine patients were alive and had their data censored when the study closed; 8 patients dying of disease related causes during the study and the remaining patients death was not disease related. Overall 2 year survival was 49% and 42% of patients were alive and progression free at 2 years. Overall survival curves are shown in Figure 2 with no significant differences seen between the three cohorts.

Limitations

As there were no dose limiting toxicities reported the study did not need to expand any of the dose cohorts which limited recruitment to 19 patients during the 25 months the study was open. This is a much smaller number than the number of eligible patients seen in the centres recruiting to the study giving the potential for selection bias to influence some of the treatment outcomes like survival.

Discussion

Despite considerable effort over the last few decades, there has been little improvement in survival for NSCLC when compared to other sites such as breast and colorectal cancers. Many reasons are documented for patients not receiving radical surgery or concurrent chemo-radiotherapy treatment[7] but in the vast majority it is due to co-morbidity, insufficient respiratory function or poor performance status. Stereotactic ablative body radiotherapy (SABR) has been developed as a treatment option for early NSCLC and is providing proof of principle evidence for accelerated dose escalation. Over the past 5 years the published evidence for SABR has increased[19,20] and consistently shows impressive local control rates of around 90% at 5 years, with evidence that this contributes to improved outcomes across a population[21]. However, there is little published randomised trial data comparing SABR with 'conventionally' fractionated radiotherapy, and the data presented has yet to show superior outcomes with SABR[22].

Van Baardwijk *et al* have performed a systematic review that extends the SABR information by including data from high dose 'conventional' radiotherapy series delivered using schedules lasting around 4 weeks[15]. These accelerated 'conventional' treatments also report good local control in stage I disease with a local relapse figure of 13%, and we should remember the median survival of 25.2 months documented for CHART treatment of stage 1A and 1B disease[23] is consistent with that reported in these publications. The significant toxicities seen when SABR was used for more central tumours[16] is an additional reason to continue to develop accelerated schedules for the treatment of stage III disease where mediastinal radiotherapy will need to be given.

Meta-analysis has confirmed that accelerated or hyper-fractionated radiotherapy schedules[6] improve local control and survival when compared to conventionally fractionated treatments (64-66Gy in 32-33 fractions), with a Hazard Ratio of 0.88 equating to a 2.5% improvement in 5 year survival. Recent NICE (National Institute for Health and Clinical Excellence) guidance[8] perceives CHART as a "gold standard" radiotherapy schedule and Din et al[24] showed that CHART results can be reproduced in daily practice with the short schedule time being popular with patients 99% of whom complete treatment and less than 1% suffering grade 4 / 5 toxicity. However, the fact remains that 61% of patients who received CHART died with persistent local disease[1].

Therefore, it is important to explore dose escalation using both CHART and other radiotherapy schedules. The recently completed RTOG 0617[11] study used a standard arm of 60Gy in 30 fractions and reported no benefit from dose escalation to 74Gy in 37 daily fractions, and patients in the higher dose arm suffered higher local relapse rates and inferior

survival compared to the control arm. While we can take the median survival of over 24 months in the standard arm to reflect contemporary practice in terms of patient selection (routine use of PET) and the availability of third and fourth line therapies for relapsed disease, we have to conclude that dose escalation that extends the treatment schedule is very unlikely to lead to any significant gains in outcomes.

However, radiobiological modelling suggests that dose escalation to improve the Tumour Control Probability (TCP) is likely to be more effective if the overall treatment time is fixed rather that the dose per fraction[25]. While designing this study we applied similar TCP modelling[26] to tentatively predict 30 month local progression free survival when treating a tumour size of around 150 cc. TCPs of 14% and 20% were calculated for 60 Gy given conventionally over 6 weeks and for CHART, the CHART study itself reporting 12 and 18% local control at 3 years[1]. These calculations also suggested that the CHART-ED schedule delivering 64.8 Gy would achieve a TCP of 47%, which compares favourably to the TCP of 42% calculated for concurrent chemo-radiotherapy delivering 66 Gy using conventional fractionation. Since the radiobiological modelling suggested that the 64.8 Gy dose would have a significant effect on local control probability we took the decision not to escalate further even though the study did not reach a MTD for the oesophagus.

The Meta-analysis by LePechoux et al [6] indicated the benefit of accelerated fractionation is not confined to the CHART schedule and dose escalation of other schedules should lead to significantly higher rates of local control than those seen with conventional fractionation. However, the results from the CHARTWEL study where the dose was escalated to 60 Gy failed to show improvement in local control feeding through to any overall survival benefits[27]. The difference in outcomes reported for CHART and CHARTWEL could be a matter of statistical chance, but factors relating to the overall length of the treatment schedule may also be in play as induction chemotherapy was routinely given prior to radiotherapy in the CHARTWEL study [27]. In addition, subgroup analysis[28] from this study does point toward improved outcomes for the accelerated schedule in populations of patients with the larger tumours where you might expect to see the most benefit.

When this study was designed, volume effects had not been demonstrated as clearly for oesophagitis as for pneumonitis. We used a volumetric dose constraint for lung, limiting V_{20Gy} to a maximum of 35% to control the rates of pneumonitis and lung fibrosis[29,30], and relied on the incrementally increasing (57.6-64.8 Gy) prescribed dose limit to control oesophageal toxicity. A time factor has been demonstrated for early mucosal reactions[31,32], and we calculated the extension of CHART to the more protracted 18 day schedule should allow higher oesophageal doses to be delivered. The maximum point cord dose in the CHART - ED

schedule was also limited to 44 Gy to allow for incomplete repair of normal tissue between RT fractions, a concern for schedules delivering three fractions each day.

The majority of patients included in our study have locally advanced NSCLC, for which neo-adjuvant, concomitant and adjuvant chemotherapy have well documented survival benefits. Consequently combined treatment is commonly recommended for this group of patients. Meta-analysis established the benefits and toxicities for conventionally fractionated radiotherapy, and the comparison of sequential with concurrent treatment produces a hazard ratio in favour of the concurrent treatment (0.84, 95% CI 0.74 – 0.95)[4] and median survivals of 24 months would now be expected in the PET staged population[11].

It needs to be remembered that the potential toxicity from the concurrent approach can be significant, with population based studies showing that performance status, age and co-morbidities exclude a high number of patients from the concurrent form of treatment[7]. The feasibility of adding induction chemotherapy to CHART has also been demonstrated by the INCH trial[17], results from which suggest this approach is associated with less toxicity than concurrent schedules.

It is in this group of patients, unsuited to concurrent chemo-radiotherapy, that the approach of sequential chemo-radiotherapy using dose escalated, accelerated radiotherapy schedules can be studied further. The UK has a depth of experience in the use of accelerated fractionations, and in addition to CHART-ED dose escalation to 64.8 Gy, similar studies for a dose-escalated 30 fraction five week concurrent CRT schedule (IDEAL-CRT)[33], and 4 week sequential CRT schedules (I-START, and Iso-IMRT) are recruiting or has just completed their recruitment. Our TCP modeling yields similar calculated TCP values (40-50%) when each of these schedules are used to deliver sequential CRT. We aim to carry out a randomized phase II trial that compares these schedules which will give some comparative data on the hypo- vs hyperfractionated approach for acceleration and aims to identifying the most appropriate dose escalated, accelerated sequential chemo-radiotherapy schedule to take into a phase III trial.

Used as a single modality treatment the CHART schedule remains a strong alternative to conventionally fractionated regimes for patients unsuitable for chemotherapy. The dose escalated CHART schedule is feasible and we saw no dose limiting toxicities up to a dose of 64.8 Gy in 42 fractions over 18 days. Given with sequential chemotherapy this schedule could be developed as an alternative in patients unable to undergo concurrent chemo-radiotherapy. We plan to take the CHARTED schedule into randomized phase II studies against dose escalated accelerated sequential chemo-radiotherapy schedules to establish the optimum method of delivering these accelerated radiotherapy regimens in the multi-modality treatment setting.

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Table 1

Demographic details for patients recruited to the CHART-ED study.

		Overall (n=18)	Group 1 (N=6)	Group 2 (N=6)	Group 3 (N=6)
Median age		70	66	74	74
Range		44-84	44-78	63-84	64-84
Males		14	4	6	4
Histology					
Squamous		16	5	6	5
Adenocarcinoma		2	1	0	1
Other		0	0	0	0
Stage (V7)	1-B	1	0	1	0
	2A / B	5	1	2	2
	IIIA	8	4	2	2
	IIIB	4	1	1	2
WHO PS	0	4	2	1	1
	1	13	4	5	4
	2	1	0	0	1
Respiratory Function					
Median FEV1		2.3	1.9	2.0	2.4
Range		1.1 to 3.6	1.1 to 3.6	1.4 to 2.6	1.6 to 2.9
Median FVC		3.5	3.0	3.3	3.5
Range		1.7 to 5.4	1.7 to 5.4	2.3 to 3.8	2.4 to 3.7
Median D_LCO		6.4	6.4	5.5	8.4
Range		1.7 to 12.0	1.7 to 12.0	3.4 to 7.4	3.8 to 8.9

Table 2

Radiotherapy planning data for patient who received a dose escalated schedule

		Group 1 (n=6)	Group 2 (n=6)	Group 3 (n=6)	All patients (n=18)
% coverage of PTV by 95% isodose	Mean	89.4	93.6	97.4	93.5
	Std dev	8.6	7.4	1.7	7.1
	Maximum	97.5	100.0	99.5	100.0
	Minimum	74.7	79.5	94.9	74.7
% whole lung V20 (Gy)	Mean	25.3	23.2	27.6	25.4
	Std dev	7.2	5.0	5.7	6.0
	Maximum	33.6	29.7	34.5	34.5
	Minimum	13.1	16.2	21.3	13.1
Maximum dose to spinal cord (Gy)	Mean	34.6	33.4	36.2	34.7
	Std dev	8.0	6.5	5.6	6.5
	Maximum	39.6	43.5	42.1	43.5
	Minimum	18.9	25.2	26.4	18.9
Gross tumour volume (GTV) (cm^3)	Mean	87.7	84.5	94.4	88.9
	Std dev	59.1	73.0	77.9	66.3
	Maximum	192.0	219.0	212.6	219.0
	Minimum	18.5	29.0	18.0	18.0
Planning target volume (PTV) (cm^3)	Mean	495.5	485.7	521.7	500.9
	Std dev	206.7	234.0	188.3	198.4
	Maximum	795.0	897.0	733.0	897.0
	Minimum	208.0	281.0	278.0	208.0
Oesophageal dose +/- 5% of prescribed		5 patients	5 patients	5 patients	

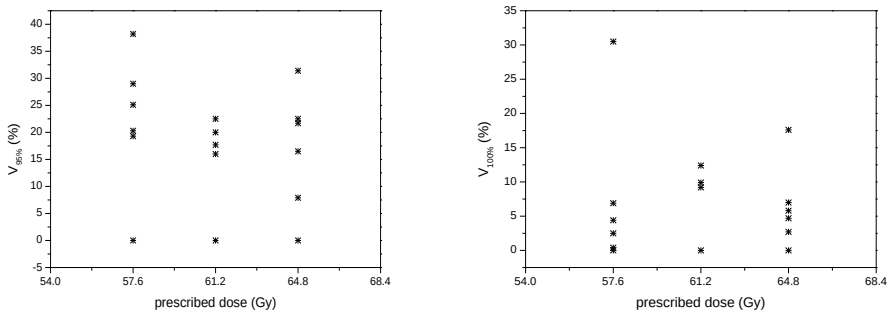
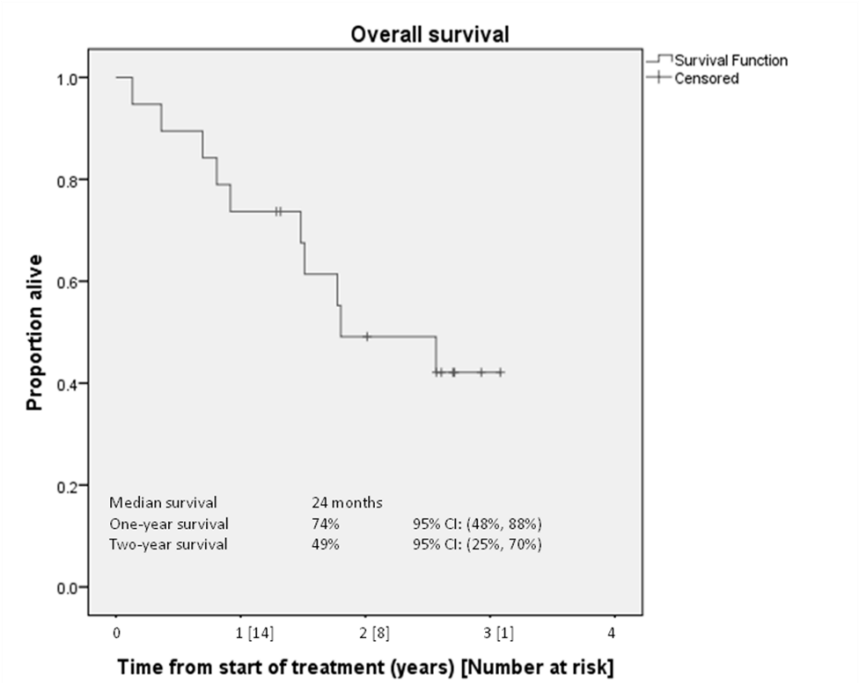


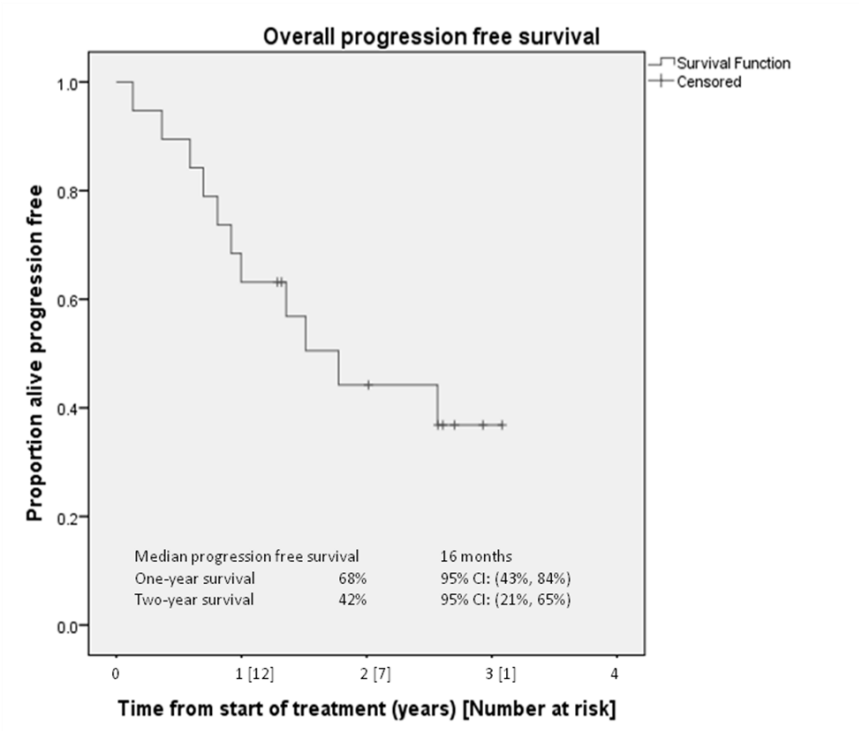
Figure 1

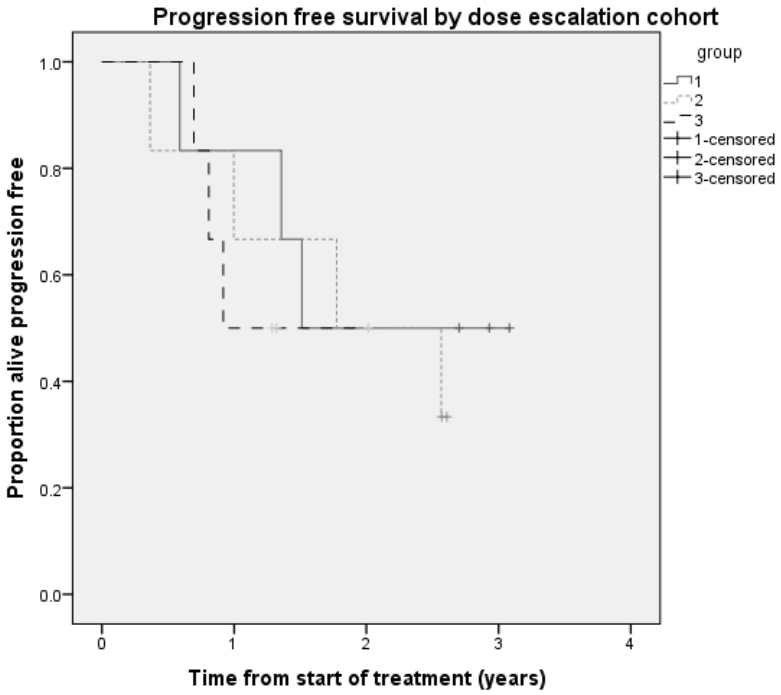
Plots showing the percentages of outlined oesophagus receiving doses in excess of (a) 95% and (b) 100% of the prescribed dose for the 18 patients treated on CHART-ED

(Nb: when points for less than 6 patients can be distinguished in these plots, it's because volumes for multiple patients lie at or very close to zero).

Figure 2. Survival graphs: overall and by dose escalation cohorts.






Progression free survival by dose escalation cohort
Proportion alive progression free
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
Time from start of treatment (years)
group
1
2
3
1-censored
2-censored
3-censored